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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/060,188
Filing Date: April 14, 1998
Appellant(s): BEHAN ET AL.

David C. Scherer
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 8 October 2010 (10/8/2010) appealing from the Office action mailed 11 September 2009 (9/11/2009).

**(1) Real Party in Interest**

The examiner has no comment on the statement at page of the Appeal Brief (of 8 October 2010) identifying by name the real party in interest in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The following is a list of claims that are rejected and pending in the application:

Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are pending and rejected.

The statement at page 3 of the Appeal Brief (of 8 October 2010) regarding the status of claims is correct.

**(4) Status of Amendments After Final**

The appellants' statement of the status of amendments after final rejection at page 3 of the Appeal Brief (of 8 October 2010) is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter at pages 3-5 of the Appeal Brief (of 8 October 2010) is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The Appellants' statement (at page 5 of the Appeal Brief of 8 October 2010) of the grounds of rejection to be reviewed on appeal is correct.

Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN

REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the Appeal Brief (of 8 October 2010) is correct.

**(8) Evidence Relied Upon**

The following is a listing of the evidence (e.g., patents, official notice, and admitted prior art) relied upon by the examiner in the rejection of claims under appeal.

Feldman, 2002. Molecular Pharmacology. 61(4): 707-709.

Janigro, 2008. Epilepsy Currents. 8(1): 23-24.

The Examiner makes the following comment regarding Appellants' Evidence Appendix (page 22 of the Appeal Brief of 8 October 2010).

The Evidence contains six Exhibits, labeled A-F. However, Appellants submitted seven Exhibits, labeled A-G, on 10/8/10 in conjunction with the Appeal Brief. Exhibits A-C filed on 10/8/10 match those listed in the Evidence Appendix. Exhibits E-G filed on 10/8/10 match Exhibits D-F listed in the Evidence Appendix. Exhibit D (Matloubian et al, 2000) does not appear on the Evidence Appendix. The Appeal Brief does not appear to refer to Matloubian et al, nor was this reference entered into the record previously. The text of the Appeal Brief refers to the Exhibits as listed in the Evidence Appendix. The Examiner has clarified which Exhibit is being referred to below in response to Appellants' arguments.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

***Claim Rejections - 35 USC § 101, utility***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are rejected under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Independent claim 69 is directed to a method for directly identifying a non-endogenous candidate compound as a compound that stimulates an endogenous G-protein coupled receptor (GPCR) or reduces the activity of an active receptor state of an endogenous GPCR, wherein an endogenous ligand for said endogenous GPCR has not been identified, said method comprising three steps (a)-(c). Step (a) requires obtaining a constitutively activated form of said endogenous GPCR, wherein said constitutively activated GPCR comprises a mutation in its amino acid sequence that increases is constitutive activity relative to said endogenous GPCR. Step (b) requires contacting the non-endogenous candidate compound with the GPCR of (a). Step (c) requires analyzing whether said non-endogenous is one that meets the goal of the preamble by measuring the ability of the candidate compound to stimulate or inhibit functionality of said constitutively activated GPCR.

Independent claim 77 is directed to a method for directly identifying a non-endogenous compound with compound efficacy as to an endogenous orphan GPCR, the method comprising four steps (a)-(d). Steps (a) and (b) are essentially the same as claim 69. Step (c) requires analyzing the functionality of the constitutively activated GPCR in the presence and absence of the non-endogenous compound. Step (d) requires identifying the non-endogenous compound as one that meets the goal of the preamble of the claim if the presence of the compound measurably alters the functionality of the constitutively activated GPCR as compared to the absence of the compound.

Claims 34, 45-52, 61, 62, 79 and 81 depend directly or indirectly from claims 66 or 77 and present further limitations to the respective claimed method.

The instant specification teaches that the structure of GPCRs was well-known in the prior art: "G protein-coupled receptors share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids which form seven alpha ('α') helixes, each of which spans the membrane. The transmembrane helixes are joined by strands of amino acids with a larger loop between the fourth and fifth transmembrane helix on the extracellular side of the membrane. Another larger loop composed primarily of hydrophilic amino acids joins transmembrane helixes five and six on the intracellular side of the membrane. The carboxy terminus of the receptor lies intracellularly with the amino terminus in the extracellular space" (page 4, lines 19-26; see also Figure 2).

The specification further teaches "[t]o date, the genetic sequence for only about 100 G protein-coupled receptors for which the activating ligand is known have been identified. However, sequences for about 100 other G protein-coupled receptor for which the activating ligand is unknown have been identified and cloned. These represent the orphan G protein coupled receptors" (page 4, line 30 through page 5, line 1). The instant specification defines the term "orphan receptor" as meaning "an endogenous receptor for which the endogenous ligand for that receptor has not been identified or is not known". Thus, the "orphan GPCR" used in claim 77 is the same as the "endogenous GPCR" used in claim 69, for which "an endogenous ligand … has not been identified". Thus, all of the claims are limited to methods of use of an endogenous GPCR for which an endogenous ligand has not been identified (i.e., an orphan GPCR). The goal of each method is to identify a non-endogenous compound as a compound that modulates (stimulates or reduces) the activity of said GPCR. The specification teaches specific mutations that can be introduced in order to constitutively activate a GPCR, regardless of whether the ligand is known. In this manner, a measurable signal of activity is produced that can be use to screen non-endogenous candidate compounds to identify those that modulate (reduce or stimulate) said activity.

As set forth in MPEP 2107.01.I.A ("Specific Utility"), a "'specific utility' is *specific* to the subject matter claimed and can 'provide a well-defined and particular benefit to the public' [citing *In re Fisher*]…This contrasts with a *general* utility that would be

applicable to the broad class of the invention. Office personal should distinguish between situations where an applicant has disclosed a specific use for or application of the invention and situations where the applicant merely indicates that the invention may prove useful without identifying with specificity why it is considered useful. For example, indicating that a compound may be useful in treating specified disorders, or that the compound has 'useful biological' properties, would not be sufficient to define a specific utility for the compound (citing *In re Kirk* and *In re Joly*)…Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition". Furthermore, MPEP 2107.01.I.B ("Substantial Utility") states, "Thus, a 'substantial utility' defines a 'real world' use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities…the following are examples of situations that require or constitute carrying out further research to identify or confirm a 'real world' context of use and, therefore, do not define 'substantial utilities': A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved. B. A method of treating an *unspecified* disease or condition. C. A method of assaying for or identifying a material that itself has no 'specific and/or substantial utility'…"

In the case *In re Fisher* (76 USPQ2d 1225 (CA FC 2005)) the U.S. Court of Appeals Federal Circuit stated, "Patent application does not satisfy utility requirement of 35 U.S.C. §101 unless it discloses both 'substantial' utility for claimed invention, in form of significant and presently available benefit to public, as well as 'specific' utility, which is well-defined and particular benefit to public" (pg 1225) and "an application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public" (pg 1230).

See also MPEP 2106, which states, the "purpose of [the utility] requirement is to limit patent protection to inventions that possess a certain level of 'real world' value, as opposed to subject matter that represents nothing more than an idea or concept, or is

simply a starting point for future investigation or research (*Brenner v. Manson*, 383 U.S. 519, 528-36, 148 USPQ 689, 693-96 (1966); *In re Fisher*, 421 F.3d 1365, 76 USPQ2d1225 (Fed. Cir. 2005); *In re Ziegler*, 992 F.2d 1197, 1200-03, 26 USPQ2d 1600, 1603-06 (Fed. Cir. 1993))." See also *Brenner v. Manson*, which states that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion".

In the instant case, the specification does not disclose a patentable utility for the "non-endogenous candidate compound" that stimulates or reduces the activity of an orphan GPCR that is identified by the claimed screening method, and therefore the claimed method lacks patentable utility. The claimed methods lack a specific and substantial utility because there is no specific and substantial utility for a non-endogenous modulatory compound identified by the claimed methods. Each orphan GPCR described in the specification for use with the claimed method lacks a specific and substantial utility. Furthermore, identification of a non-endogenous compound that can stimulate (i.e., agonize) or inhibit (i.e., antagonize) the activity of an orphan receptor does not provide a specific and substantial utility for such an identified compound. The specification teaches that such compounds may prove useful without identifying a specific use for the stimulation or inhibition of particular orphan GPCRs. The specification does not provide a reasonable correlation between the activity of any of the orphan GPCRs and a specific and substantial use (e.g., treatment of a disease associated with the activity of the GPCR). The specification merely suggests that once a compound is identified that modulates the activity of a receptor (e.g., an inverse agonist that reduces the activity of a constitutively activated receptor), that such compounds can then be used as "lead compounds in drug discovery programs for treating diseases related to receptors" (page 33, lines 20-24). Such represents "further research" that must be performed such that the invention is useful "at some future date" (as per *In re Fisher*, cited above). The specification provides no evidence or other guidance that would lead the skilled artisan to conclude that any orphan GPCR to be used in the claimed method is likely to be involved with any particular disease, such that a

modulator of the compound identified by the claimed method could be used for treatment of such disease.

In summary, the proposed uses of the claimed invention to identify non-endogenous compounds that modulate the activity of orphan GPCRs requires further research to identify a specific and substantial use for the identified compound. Therefore, the application fails to provide guidance as to how one of skill in the art could use the claimed method in a way that constitutes a specific and substantial utility. Those skilled in the art would conclude that the specification does not disclose a substantial utility for the claimed method, i.e., an invention that is useful to the public in its current form, rather than potentially useful in the future after further research, per *In re Fisher*.

### *Claim Rejections - 35 USC § 112, 1st paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

For the reasons described above in the section “Claim Rejections – 35 USC § 101”, the claimed invention is not supported by a specific and substantial asserted utility, and therefore one skilled in the art would not know how to use the claimed invention without undue experimentation.

**(10) Response to Argument**

Appellants' arguments (pages 5-17 of the Appeal Brief filed on 8 October 2010) are addressed by section in the order presented by Appellants.

***I. Appellants' arguments that claims 34, 45-52, 61, 62, 69, 77, 79 and 81 have a patentable utility under 35 U.S.C. § 101* (pages 5-17)**

At pages 5-6, Appellants discuss the procedures for applying a rejection under 35 U.S.C. § 101, citing the 2001 USPTO Utility Examination Guidelines; *Juicy Whip Inc. v. Orange Bang Inc.*; *In re Langer* and MPEP § 2107. No particular statements are disputed.

At page 7, first paragraph, Appellants summarize their arguments for utility of the claimed invention: the application fully discloses "some identifiable benefit" for the claimed invention; that the "totality of the evidence demonstrates an asserted utility and a well-established utility that are specific, substantial and credible for the claimed invention", and that evidence has been provided that it is more likely than not that the statements of utility are false.

These arguments have been fully considered but are not found to be persuasive. Each of Appellants' specific arguments is addressed below, and each is not found to be persuasive. Thus, the subject application does not disclose some identifiable benefit for the claimed invention, and it is maintained that the claimed invention does not meet the requirements under 35 U.S.C. § 101.

At page 7, second paragraph, Appellants argue that the claimed methods are applicable to any orphan GPCR that can be mutated to achieve constitutive activity, and should not be "limited to one particular orphan GPCR or to a particular disease or disorder". Appellants argue that one of ordinary skill in the art practicing the claimed method would "have in hand an orphan GPCR associated to their satisfaction, e.g., one that is associated with a particular cellular function, disease or disorder".

Appellants' arguments have been fully considered but are not found persuasive. The claims have not been rejected because they are not limited to a particular orphan GPCR or to a particular disease or disorder. Instead, the claims have been rejected because they are directed solely to a method of identifying non-endogenous compounds for which there is no specific and substantial utility once identified. This is because said compounds modulate the activity of uncharacterized orphan receptors and this activity has not been associated with any particular, immediate use (e.g.,

treatment of a specific disease associated with the activity of a specific orphan receptor). With respect to a person of ordinary skill in the art "having in hand" an orphan GPCR associated with a particular cellular function, disease or disorder when practicing the claimed invention, this represents "further research" as set forth *In re Fisher (*pg 1230, quoted above in the rejection). To reiterate, "[a]n application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public" (*In re Fisher*, pg 1230, also quoted above).

At page 7, third paragraph, Appellants describe the claimed invention in view of the prior art, and argue that the specification teaches that the claimed method solves the problem of identifying "pharmacologically effective compounds for regulation of receptor activity even in the absence of any prior knowledge about the endogenous ligand".

Appellants' arguments have been fully considered but are not found persuasive. It is not disputed that the claimed methods will identify non-endogenous compounds that modulate (stimulate or reduce) the activity of a constitutively activated orphan receptor. However, the specification does not teach any specific and substantial "pharmacologically effective" use for such modulators. Again, the identification of such use represents "further research" that must be completed in order for the invention to prove useful at some future date.

At page 8, first and second paragraphs, Appellants quote a portion of the rejection at page 4 of the 9/11/2009 Office Action, argue that the rejection errs in its characterization of the requirements for establishing utility, and contend that the claimed invention has a specific and substantial utility.

Appellants' arguments have been fully considered but are not found persuasive. In this paragraph, Appellants do not point out any specific errors in the quoted section of the 9/11/2009 Office Action, and the statements contained therein are maintained. Each of Appellants' specific arguments are addressed herein (either above or below), and

each is not found to be persuasive. Thus, the subject application does not disclose a specific and substantial utility for the claimed invention, and it is maintained that the claimed invention does not meet the requirements under 35 U.S.C. § 101.

In the paragraph bridging pages 8 and 9, Appellants argue that knowledge of the natural ligand of a GPCR is not necessary for establishing a useful function for such a receptor. Appellants argue pharmaceutical agents can be developed and marketed based on a receptor's function even in the absence of the natural ligand. Appellants argue that this is "exemplified by the fact that numerous opioids having analgesic functionality at the mu-opiate receptor were identified and developed long before the first endogenous agonists of that receptor were discovered in 1975".

Appellants' arguments have been fully considered but are not found persuasive. The specification does not demonstrate a useful function for an orphan GPCR encompassed by the claims. The specification does not teach any specific and substantial "pharmaceutical" use for an agent that modulates a receptor in absence of the knowledge of its natural ligand. Again, the identification of such "pharmaceutical" use represents "further research" that must be completed in order for the invention to prove useful at some future date. With respect to the mu-opiate receptor, an endogenous agonist for this receptor was identified in 1975. Thus, the mu-opiate receptor does not provide support for the claimed invention because at the time of filing of the instant application it was not an orphan receptor and thus is not encompassed by the claimed invention. Furthermore, the various mammalian mu-opiate receptors were not cloned until the early 1990s. Thus, mutated versions of the receptors could not have been made until well after the endogenous ligand for receptor was identified. Thus, the status of the receptor prior to 1975 as an orphan receptor for which a non-endogenous ligand was identified is not germane to the claimed invention, as the claimed invention could not be practiced with said receptor.

At page 9, first full paragraph through page 10, first full paragraph, Appellants argue that the claimed methods, as well as the compounds identified by said methods, have a specific and substantial utility because "prior to the time of filing the present application, orphan GPCRs having a specific function or activity had been identified"

(page 9). In support of this argument, Appellants point to the teachings of three publications: Liao et al (1997), Alkhatib et al (1997) and Farzan et al (1997). Appellants argue that these references disclose that the orphan receptors STRL33 (Liao et al; Alkhatib et al), gpr1 and gpr15 (Farzan et al) are co-factors for retroviral entry into cells.

These arguments have been fully considered but are not found to be persuasive. The known function of STRL33, gpr1 and gpr15 as fusion co-factors for retroviral entry into cells does not provide a specific and substantial utility of the compounds that modulate (stimulate or reduce) the constitutive activity identified by the claimed method. The co-factors can bind a complex of retrovirus and CD4 and mediate entry of the retrovirus, whereas the instant claims are directed to method of screening for modulators of the constitutive activity of the receptors. The instant specification does not establish any correspondence between the use of modulators of the claimed invention and the role of STRL33, gpr1 and gpr15 in retroviral entry. For instance, it is not clear how modulators of the constitutive activity of STRL33, gpr1 and gpr15 activity would be used in relation to retroviral co-entry, which is not taught by Liao et al, Alkhatib et al, or Farzan et al to involve the GPCR activity. Furthermore, these receptors are not disclosed in the instant specification, and use of modulators in blocking retroviral entry is not taught as a utility for modulators of the instant invention. Determining if such a correspondence exists would constitute carrying out further research to identify or reasonably confirm a “real world” context of use.

At page 10, second full paragraph, and further in the paragraph bridging pages 10-11, Appellants further respond to the above arguments. Appellants submit that any lack of disclosure in the specification "regarding STRL33, gpr1 and gpr15 as co-factors for retroviral entry into cells is immaterial to Appellants arguments support the well-established utility of the claimed invention". Appellants argue that "a patent does not have to include everything known in the art at the time of filing" (citing *Hybritech Inc. v. Monoclonal Antibodies* (1986)).

These arguments have been fully considered but are not found to be persuasive. The role of the orphan GPCRs STRL33, gpr1 and gpr15 as co-factors for retroviral entry into cells while known in the art at the time of filing does not provide a well-established

utility for the claimed method. The references of Liao et al, Alkhatib et al, or Farzan et al do not provide a well-established role for the activity of STRL33, grp1 or gpr15, such that a compound that modulates (stimulate or reduce) the activity of one of these receptors that is identified by the claimed method could be use for a specific and substantial activity (e.g., treatment of HIV). Instead, as set forth above, the teachings of these references fails to provide any correspondence between the use of modulators of the claimed invention and the role of STRL33, gpr1 and gpr15 in retroviral entry. It is not clear from the teachings of the art how modulators of the constitutive activity of STRL33, gpr1 and gpr15 activity would be used in relation to retroviral co-entry, which is not taught by Liao et al, Alkhatib et al, or Farzan et al to involve the GPCR activity.

At page 11, first and second full paragraphs, Appellants dispute that STRL33, gpr1 and gpr15 are not receptors encompassed by the claims at the time of filing because they are not orphan GPCRs. Appellants argue that CD4 is not a ligand of STRL33, gpr1 or gpr15 despite the binding of said receptors to a virus that simultaneously binds to CD4. Appellants further argue that while "a virus, which is a non-endogenous entity employs CD4 as a primary receptor and one of the above-cited orphan GPCRs as a co-receptor" this does not mean that CD4 is an endogenous ligand for that receptor. Appellants argue that CD4 is not taught to bind the receptor alone, and is not taught to be an endogenous ligand by the cited references.

These arguments have been fully considered but are not found to be persuasive. As argued previously, the orphan receptors STRL33, gpr1 and gpr15 are not receptors encompassed by the claims at the time of filing. Claim 69 requires that "an endogenous ligand for said endogenous GPCR has not been identified" and claim 77 requires an "endogenous orphan GPCR" (i.e., a GPCR for which the endogenous ligand has not been identified). The specification defines the term "endogenous" as "shall mean a material which a mammal naturally produces" (pg 18, line 22) and "ligand" as "shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor" (pg 22, lines 4-5). The previously submitted references provide evidence of identification of an endogenous, naturally occurring molecule specific for each of STRL33, gpr1, and gpr15. Farzan et al (1998; Exhibit B) teaches

that "The gp120 [viral] glycoprotein binds the CD4 molecule, following which the gp120-CD4 complex binds one of the members of the chemokine receptor subgroup of seven-transmembrane segment (7-TMS) receptor" (pg 405). Farzan et al further identifies the 7-TMS receptors gpr1 and gpr15 as "coreceptors for SIV [simian immunodeficiency virus]". Thus, Farzan et al teach that the gp120-CD4 complex binds to each of gpr1 and gpr15. Farzan et al do not teach whether or not the CD4 portion of the complex binds directly to gpr1 or gpr15, but the term "specific" encompasses either direct or indirect binding through a second molecule (i.e., the gp120-CD4 complex "specifically" binds to gpr1 or gpr15 as opposed to binding to most other cell surface molecules). The CD4 component of this complex is a material which a mammal naturally produces, and thus meets the definition of endogenous in the instant specification. Thus, Farzan et al teach an endogenous, naturally occurring molecule (CD4) specific for gpr1 and gpr15. Thus, gpr1 and gpr15 are not receptors as defined by the instant claims. Similarly, Liao et al (1997; Exhibit B) teaches that STRL33 is a cofactor for HIV entry in cells expressing CD4; thus CD4 is an endogenous ligand for STRL33. Thus, at the time of filing of the instant application neither of STRL33, gpr1 or gpr15 was a receptor as encompassed by the instant claims.

Furthermore, the specification (page 18, line 22 through page 19, line 1) teaches that the term "ENDOGENOUS in reference to, for example and not limitation, the term 'receptor' shall mean that which is naturally produced by a mammal ... or a virus" (emphasis added). Thus, the term "endogenous ligand" when used in reference to a receptor does not exclude a ligand to a receptor, wherein the ligand is produced by a virus. Thus, HIV itself is an endogenous ligand of STRL33, gpr1 and gpr15 according to the definitions of the instant specification, and for this reason also, at the time of filing of the instant application neither of STRL33, gpr1 or gpr15 was a receptor as encompassed by the instant claims.

In the paragraph bridging pages 11 and 12, and further in the first full paragraph on page 12, Appellants argue that the specification provides a teaching for associating receptors and diseases and disorders. Appellants point to page 33, line 20 to page 34, line 12, (and provide an excerpt of such) and page 75, line 20 to page 76, line 1 (not

quoted, but appears to summarize the quoted excerpt). Appellants argue that the claimed method provides inverse agonists of orphan GPCRs that can be correlated with specific diseases, allowing "for a rational approach to the development of a pharmaceutical composition(s) for such diseases" (page 12).

These arguments have been fully considered but are not found to be persuasive. The specification does not teach any specific and substantial "pharmaceutical" use for a composition comprising an agent that modulates an orphan GPCR. The identification of such "pharmaceutical" use represents "further research" that must be completed in order for the invention to prove useful at some future date, as does the identification of an association of a GPCR with a specific disease.

At page 12, third full paragraph, Appellants argue that "the specification describes an example of an orphan GPCR (GPR3) that is associated with a disease (epilepsy)" which provides utility for a method of screening with using said GPCR. Appellants point to Figure 15 and Example 4 as showing that GPR3 is more highly expressed in neuronal tissue from the temporal lobe of individuals with epilepsy as compared to individuals not suffering from this condition.

These arguments have been fully considered but are not found to be persuasive. First (as pointed out in the Office Action of 9/11/09), GPR3 is not encompassed by the instant claims, as it is an endogenously constitutively active GPCR (i.e., naturally constitutively activated) and the claims require a GPCR that has been constitutively activated by mutation. Second (as also set forth 9/11/09), the association of GPR3 with a specific disease (epilepsy) does not provide a specific and substantial utility for a method of screening for a compound that modulates (stimulates or reduces) GPR3 activity even if such were encompassed by the instant claims. While measurement of increased GPR3 expression could possibly be used to confirm a diagnosis of epilepsy, this finding does not provide a use for agonists or antagonists of GPR3 identified by the claimed methods. The overexpression of GPCR in tissue from a person with a particular disease does not reasonably indicate that increased activity of said GPCR is a cause of the disease rather than a consequence. For example, with respect to GPCR perturbations in the disease hypertension, "it has been difficult to determine whether

they are the cause or consequence of the disease" (Feldman, 2002. Molecular Pharmacology. 61(4): 707-709; cited previously). With respect to temporal lobe epilepsy, Janigro (2008. Epilepsy Currents 8(1): 23-24; cited previously) teaches that "[a]s with many pathological findings in neurodegenerative diseases, it is difficult to determine if the changes are a cause or consequence of epileptic seizures" (pg 23). As such, at the time of filing it would have required further research for the skilled artisan to confirm that increased GPR3 activity plays a role in epilepsy, such that administration of an antagonist could be used to treat epilepsy. Thus, it would have required further research for the skilled artisan to identify or confirm a “real world” context of use for the agonists and antagonists of GPR3 identified by methods of screening for such.

At page 12, fourth full paragraph, Appellants argue that the utility of the claimed invention can be supported by the association with an orphan GPCR with a "specific cellular process" in either the specification or well-known in the art at the time of filing. Appellants point to STRL33, gpr15 and gpr1 as being described in the art and GPR3 as being described in the specification in a manner that makes the claimed invention useful.

These arguments have been fully considered but are not found to be persuasive. Appellants' arguments regarding STRL33, gpr15, gpr1 and GPR3 are addressed above, and it is maintained that neither the teachings of the specification, nor the teachings of the art, provide a utility for the claimed invention.

At page 13, first and second full paragraphs, Appellants further argue that the skilled artisan would not make the effort to screen an orphan GPCR if they did not have some use for the compounds identified by the screening method. Appellants argue that the claimed method allows a user to identify specific compounds that have a defined modulatory activity for an orphan GPCR of interest, which is a specific and substantial "real world" use, regardless of the reason for why it is of interest to a user. Appellants argue that the utility is in providing a means to by-pass a bottleneck in the orphan GPCR field that results from "waiting for an orphan GPCR to be 'de-orphanized' prior to conducting further functional studies" (page 13, first full paragraph). Appellants argue that "finding an endogenous ligand for an orphan receptor was, and still is, very

expensive, time consuming and oftentimes unsuccessful" (page 13, second full paragraph).

These arguments have been fully considered but are not found to be persuasive. The argument that the instant invention can "by-pass the significant bottle-neck in the orphan GPCR filed" by de-orphanizing a receptor is merely a restatement of the argument that the claimed invention is a "research tool" (which is addressed below) and does not provide a specific and substantial utility for the claimed invention at the time of filing. Furthermore, any benefits of "by-passing a bottleneck" with regard to expense, time or success of identifying non-endogenous modulating compounds of orphan receptors does not obviate the requirement for a specific and substantial use for the compounds once identified, and the lack of utility for such when "further research" is required.

At page 13, second full paragraph through page 14, first full paragraph, Appellants argue that the claimed method can be considered a "research tool". Appellants point to MPEP 2107.01(C), heading "Research Tools". Appellants argue that this section states that "research tools that are used in a research or laboratory setting" have "a clear, specific and unquestionable utility" and that instant invention is such a research tool.

Appellants' arguments have been fully considered but are not found persuasive. Appellants' arguments include statements taken from Section "C. Research Tools" of MPEP 2107.01 but do not address other statements founds in the same section. Specifically, the same section also states that "[a]n assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact 'useful' in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as 'research tool,' 'intermediate' or 'for research purposes' are not helpful in determining if an applicant has identified a specific and substantial utility for the invention". As set forth in the above rejection, in the instant case further research would be required to identify a specific and substantial use for modulating compounds

identified by the claimed method, which is limited to a method of using orphan GPCRs. Therefore, the claimed method lacks a specific and substantial utility. Thus, Appellants' arguments that the instant invention has utility solely because it is a "Research Tool" are not persuasive.

At page 14, second to fourth full paragraphs, Appellants argue that the "real world" utility and significance of the claimed invention is appreciated by investors and biotechnology companies. In support, Appellants point to two press releases from the assignee Arena Pharmaceutical, released 2/22/99 (referred to as "Exhibit D" in the Appeal Brief including the Evidence Appendix; mislabeled as "Exhibit E" on the document itself) and 11/15/99 (referred to as "Exhibit E" in the Appeal Brief including the Evidence Appendix; mislabeled as "Exhibit F" on the document itself).

Appellants' arguments have been fully considered but are not found persuasive. Patentable utility is not measured by commercial interest. A discovery or idea may generate commercial interest simply in hopes that after further research is performed a specific and substantial utility may be identified.

At page 15, first full paragraph, Appellants argue that the European Patent Office considers the claims to have "clear industrial application". In support, Appellants point to "a copy of the claims that have been granted in the European counterpart to the subject application" (referred to as "Exhibit F" in the Appeal Brief including the Evidence Appendix; mislabeled as "Exhibit G" on the document itself).

Appellants' arguments have been fully considered but are not found persuasive. The standards for utility (or "industrial application") as determined by the European Patent Office may be different from the utility requirement of 35 U.S.C. § 101. Therefore, any decision made by the European Patent Office is not determinative of the utility of the claimed methods of the instant application.

At page 15, second full paragraph, Appellants argue that the claimed methods identify compounds that "can be employed in a predictable manner as reagents that have a known effect on the orphan GPCR (i.e., as agonists of inverse agonists)" and that the identified compounds have as much immediate utility as would the endogenous ligand for the receptor because they can be employed in "a predictable manner as

reagents that have a known effect on the orphan GPCR (e.g., as agonists or inverse agonists)" and thus no further experiments are required for the claimed screening method to have utility (pg 9).

Appellants' arguments have been fully considered but are not found persuasive. The identification of modulatory compounds from a group of candidate compounds does not provide an immediate, real-world utility for the method of screening in absence of an immediate real-world use for said modulatory compound once identified. The fact that said modulatory compounds can be employed in a predictable manner to modulate the orphan receptor does not provide an immediate, real-world utility for said modulation; said modulation would be performed predictably for no purpose other than "further research".

At page 15, third full paragraph, Appellants further argue that "as with sequencing assays, and/or PCR assays, the user of the claimed screening assay determines which specific entity is the subject of the analysis (i.e., which specific orphan GPCR is to be employed to identify modulatory compounds)", and that the reasons for screening for modulatory compound of a particular orphan receptor will vary. Appellants argue that regardless of the reasons, "the MPEP citation above clearly and explicitly states that screening assays have a 'clear, specific and unquestionable utility'".

Appellants' arguments have been fully considered but are not found persuasive. The "MPEP citation above" is presumed to be Section "C. Research Tools" of MPEP 2107.01 was addressed above. The ability of the user of the screening assay (i.e., a person of ordinary skill in the art) to choose the orphan GPCR to be employed does not provide utility for the claimed method in the absence of any orphan GPCRs with specific and substantial utility to be chosen. Unlike the claimed method, which is limited to orphan GPCRs without utility themselves, sequencing and PCR assays can be performed with nucleic acids with or without utility; the nucleic acids with utility providing a use (in accord with 35 U.S.C. § 101) for such methods. The argument that there are a "variety" of reasons for screening for a modulatory compound of a particular orphan receptor is a vague statement that does not provide a specific and substantial use for an identified modulatory compound of a particular orphan receptor.

At page 16, first full paragraph, Appellants provide further arguments regarding PCR. Appellants argue that the claimed methods have utility in that they can be applied to any orphan GPCR, as sequencing assays and PCR can be applied to any polynucleotide of interest.

Appellants' arguments have been fully considered but are not found persuasive. The claimed methods are limited solely to a genus of "orphan receptors" that lacked utility at the time of fling of the instant application. At the time of invention of PCR in 1983, many nucleic acid sequences existed that either had utility as markers or to encode specific proteins with utility. Thus, at the time of invention, PCR had immediate utility in producing large quantities of identical copies of nucleic acids with specific and substantial utility. In contrast, the instantly claimed methods are limited solely to identifying non-endogenous compounds that modulate (stimulate or reduce) the activity of "orphan GPCRs" (i.e., a GPCR for which an endogenous ligand has not been identified). There is no specific and substantial utility for any of the non-endogenous compounds identified by the claimed methods. Further research would be required to identify a use for any of the compounds identified by the claimed methods.

At page 16, second full paragraph, Appellants argue that non-endogenous compounds identified by the claimed methods do have specific and substantial utility, because orphan GPCRs have been associated with specific functions or cellular processes, as detailed in the specification as filed and known in the art at the time of filing, and regardless of "the current status of the receptor (i.e., if it has since been de-orphanized by identification of its endogenous ligand)".

Appellants' arguments have been fully considered but are not found persuasive. Here it is assumed that Appellants again refer to STRL33, gpr15, gpr1 and GPR3, because Appellants have asserted no other particular GPCRs associated with specific functions or cellular functions. Appellants' arguments regarding STRL33, gpr15, gpr1 and GPR3 are addressed above, and it is maintained that neither the teachings of the specification, nor the teachings of the art, provide a utility for the claimed invention.

In the paragraph bridging pages 16 and 17, Appellants argue against the analogy of the claimed invention to a gene chip in which none of the genes is characterized.

Appellants argue that "the *possibility* of producing a gene chip with no characterized genes in no way negatively impacts the broad utility of gene chips"; i.e., that a species of the claimed invention "might fail a specific test of utility does not mean the entire generic claim lacks utility". Appellants argue that orphan GPCRs can and have been characterized and thus are not akin to uncharacterized genes. Appellant argue that because orphan receptors have been identified that are associated with an activity, disease or cellular function, the claimed screening methods are useful.

Appellants' arguments have been fully considered but are not found persuasive. The claimed invention was not compared to a "gene chip" in general, but rather to a gene chip with no characterized genes. If the claimed method encompassed all GPCRs, (including non-orphan GPCRs with known ligands), it would have utility. Instead, the claimed method is limited to orphan GPCRs. These claimed methods are analogous to a gene chip in which none of the genes on the chip is a characterized gene. In general, gene chips are commercially successful and the skilled artisan would believe them to be useful. However, a gene chip would not meet the utility requirement if none of the genes on the chip had a specific and substantial utility.

***II. Appellants' arguments that claims 34, 45-52, 61, 62, 69, 77, 79 and 81 are enabled under 35 U.S.C. § 112, first paragraph*** **(page 5-17)**

At page 17, Appellants "submit that the rejection of the claims for lack of utility has been adequately addressed in the arguments in the preceding section of this Appeal Brief (i.e., Appellants arguments in support of utility of the claimed invention under 35 U.S.C. § 101)" and therefore "request reversal of the rejection of the claims as unpatentable under 35 U.S.C. §112, first paragraph".

Appellants' arguments have been fully considered but are not found persuasive. Appellants' arguments in support of utility of the claimed invention under 35 U.S.C. § 101 are addressed above. For the reasons described above, in the section "Claim Rejections – 35 USC § 101", the claimed invention is not supported by a specific and

substantial asserted utility, and therefore it is maintained that one of skill would not know how to use the claimed invention without undue experimentation.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Z. C. H./

Examiner, Art Unit 1646

Conferees:

/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646

/Kay Kim/

Primary Patent Examiner